Afrezza (Insulin Human) Inhalation Powder Approved for the Treatment of Patients with Type 1 or Type 2 Diabetes

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Diabetes is a chronic disease that is often accompanied by multiple comorbidities and health complications.[1] In the United States, diabetes affects an estimated 29.1 million people—approximately 9.3% of the US population.[1] An additional 37% of adults aged ≥20 years are estimated to have prediabetes, based on 2009-2012 data for fasting glucose or glycated hemoglobin (Hb) A_{1c}.[1] Furthermore, with the aging of the US population during the next few decades, the prevalence of diabetes is projected to increase from 1 in 10 adults today to a staggering 1 in 3 adults by 2050.[2]

In 2010, the American Diabetes Association (ADA) adopted the criterion of HbA_{1c} levels ≥6.5% for a diagnosis of diabetes.[3] Approximately 5% of all cases of diabetes are type 1 diabetes mellitus, and 90% to 95% of all cases are type 2 diabetes mellitus.[1]

Diabetes is the seventh leading cause of mortality in the United States. In fact, the death rate for patients with diabetes is 1.5 times higher than for individuals without diabetes.[1] Aside from being a major cause of heart disease and stroke, diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among US adults.[1] Moreover, patients with diabetes have an increased risk for other complications, including nerve disease, nonalcoholic fatty liver disease, periodontal disease, erectile dysfunction, hearing loss, depression, and pregnancy complications compared with individuals without diabetes.[1]

The annual US healthcare costs attributed to diabetes totaled $245 billion in 2012, including $176 billion in direct medical costs and $69 billion in reduced productivity (eg, increased absenteeism, reduced productivity, lost productivity resulting from early mortality, and the inability to work resulting from disability).[4] These 2012 costs represent a 41% increase from the $174 billion in diabetes-related costs in 2007. Overall, the medical expenses for patients with diabetes are 2.3 times higher than expenses for individuals without diabetes.[4]

The management of diabetes is complex, generally requiring multiple risk-reduction strategies in addition to glycemic control.[2] This demands an ongoing approach that considers the whole patient—glycemic control to prevent or reduce microvascular complications, as well as strategies to address obesity and prediabetes as underlying risk factors for diabetes and related macrovascular complications. These approaches often include dietary and other behavioral and lifestyle changes.[5]

The adequate control of HbA_{1c} levels has been shown to reduce diabetes-associated morbidity and mortality by decreasing chronic complications.[6] In fact, a 1% reduction in HbA_{1c} levels is associated with a 35% reduction in diabetes-related microvascular complications, including diabetic neuropathy, nephropathy, and retinopathy.[6]

The ADA recommends a general target HbA_{1c} level of <7% for adults with diabetes, based on a 2013 position statement on the standards of care for diabetes.[6] According to the ADA, the stringency of this goal may need to be adapted based on the patient's duration of diabetes, comorbidities, age, known cardiovascular or advanced microvascular complications, and other patient-specific factors.[6]

In a 2013 consensus statement, the American Association of Clinical Endocrinologists (AACE) recommended an HbA_{1c} target goal of <6.5% in the majority of patients with type 2 diabetes, acknowledging that this goal may be too aggressive for some patients and not aggressive enough for others (ie, younger patients for whom a lower target may prevent later complications).[5] The AACE also states that the goals of lifestyle modification and antihyperglycemic pharmacotherapy should aim to (1) achieve clinical and biochemical glucose targets, (2) avoid hypoglycemia, (3) reduce or avoid increasing cardiovascular risk, and (4) assist with weight loss and minimize weight gain in patients who are obese.[5]

Although progress has been made in the number of US patients who achieve the target HbA_{1c} level of <7%, there remains a marked need for improvement.[7] Ongoing clinical management, patient engagement, education, and the development of novel therapies may help to improve the achievement of glycemic control targets and outcomes for patients with diabetes.

FDA Approves Insulin Human Inhalation Powder

On June 27, 2014, the US Food and Drug Administration (FDA) approved insulin human inhalation powder (Afrezza; MannKind Corporation), a rapid-acting

inhaled insulin that is used to improve glycemic control in adults with diabetes.[8]

Insulin human inhalation powder is delivered via an inhaler that can be used for up to 15 days from the date of first use. In patients with type 1 diabetes, insulin human inhalation powder must be used with a long-acting insulin. Insulin human inhalation powder is not recommended for the treatment of diabetic ketoacidosis and is not recommended in patients who smoke.[9]

"Afrezza is a new treatment option for patients with diabetes requiring mealtime insulin," said Jean-Marc Guettier, MD, Director of the FDA's Division of Metabolism and Endocrinology Products. "Today's approval broadens the options available for delivering mealtime insulin in the overall management of patients with diabetes who require it to control blood sugar levels."[8]

Mechanism of Action

The new medication is a rapid-acting inhaled insulin. Insulin lowers HbA_{1c} levels by stimulating peripheral glucose uptake via skeletal muscle and fat and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in adipocytes, inhibits proteolysis, and enhances protein synthesis.[9]

The insulin contained in this new inhalation powder is regular human insulin. After pulmonary absorption into systemic circulation, the metabolism and elimination of this new insulin powder are comparable with regular human insulin. The peak insulin levels were achieved within 12 to 15 minutes after administration of insulin human inhalation powder, with serum insulin concentrations declining to baseline levels by approximately 180 minutes.[9]

Dosing and Administration

Insulin human inhalation powder is available as single-use cartridges of 4 and 8 units.[9] This medication is administered at the beginning of a meal using a single inhalation per cartridge. Dosing must be individualized. Before administering insulin human inhalation powder, a detailed medical history, physical examination, and spirometry (to assess pulmonary function) must be conducted in all patients to identify potential lung disease.[9]

Clinical Trials

The safety and efficacy of insulin human inhalation powder were studied in 3017 adults with diabetes, including 1026 patients with type 1 diabetes and 1991 patients with type 2 diabetes.[8,9] Its efficacy in patients with type 1 diabetes was compared with insulin aspart in combination with basal insulin. In patients with type 2 diabetes, insulin inhalation powder was studied in combination with oral antidiabetes drugs; its efficacy in patients with type 2 diabetes was compared with placebo inhalation.[9]

With the approval of insulin human inhalation powder, the FDA requires a Risk Evaluation and Mitigation Strategy program that includes a communication plan informing healthcare professionals about the drug's association with the serious risk of acute bronchospasm.[8] The FDA also requires several postmarketing studies, including a clinical trial to evaluate the drug's safety and efficacy in pediatric patients; a clinical trial to assess the potential risk of pulmonary malignancy and the cardiovascular risk and long-term effects on pulmonary function; and 2 pharmacokinetic and pharmacodynamic euglycemic glucose clamp clinical trials (ie, 1 clinical trial to assess dose response and 1 clinical trial to assess within-subject variability).[8]

Type 1 Diabetes

A 24-week, open-label, active-controlled study investigated the glucose-lowering effect of mealtime insulin human inhalation powder used in combination with a basal insulin in patients with inadequately controlled type 1 diabetes. After a 4-week basal insulin optimization

Table 1 Mealtime Insulin Human Inhalation Powder plus Basal Insulin versus Insulin Aspart plus Basal Insulin in Adults with Type 1 Diabetes: Week 24

Efficacy parameter	Insulin human inhalation powder + basal insulin (N = 174)	Insulin aspart + basal insulin (N = 170)
HbA_{1c} level		
Baseline, adjusted mean, %	7.94	7.92
Change from baseline, adjusted mean,[a] %	–0.21	–0.40
Difference from insulin aspart, adjusted mean,[a] %	0.19 (95% CI, 0.02 to 0.36)	
Patients achieving HbA_{1c} ≤7%, %[b]	13.8	27.1
Fasting plasma glucose		
Baseline, adjusted mean, mg/dL	153.9	151.6
Change from baseline, adjusted mean,[a] mg/dL	–25.3	10.2
Difference from insulin aspart, adjusted mean,[a] mg/dL	–35.4 (95% CI, –56.3 to –14.6)	

[a]Data at 24 weeks were available from 131 patients receiving insulin human inhalation powder and 150 patients receiving insulin aspart.
[b]This percentage was calculated based on the number of patients randomized in the clinical trial.
CI indicates confidence interval; HbA_{1c}, glycated hemoglobin.
Source: Afrezza (insulin human) inhalation powder prescribing information; June 2014.

Table 2 Insulin Human Inhalation Powder versus Placebo in Adults with Type 2 Diabetes Inadequately Controlled with Oral Agents: Week 24

Efficacy parameter	Insulin human inhalation powder + antidiabetic agents (N = 177)	Placebo + oral antidiabetic agents (N = 176)
HbA_{1c} level		
Baseline, adjusted mean, %	8.25	8.27
Change from baseline, adjusted mean,[a] %	–0.82	–0.42
Difference from placebo, adjusted mean,[a] %	–0.40 (95% CI, 0.57 to –0.23)	
Patients achieving HbA_{1c} ≤7%, %[b]	32.2	15.3
Fasting plasma glucose		
Baseline, adjusted mean, mg/dL	175.9	175.2
Change from baseline, adjusted mean,[a] mg/dL	–11.2	–3.8
Difference from placebo, adjusted mean,[a] mg/dL	–7.4 (95% CI, –18.0 to 3.2)	

[a]Data at 24 weeks were available from 131 patients receiving insulin human inhalation powder and 150 patients receiving insulin aspart.
[b]This percentage was calculated based on the number of patients randomized in the clinical trial.
CI indicates confidence interval; Hb, hemoglobin.
Source: Afrezza (insulin human) inhalation powder prescribing information; June 2014.

period, 344 patients were randomized to receive either insulin human inhalation powder or insulin aspart, administered at each meal of the day. Mealtime insulin doses were titrated to glycemic goals for the first 12 weeks, and were kept stable for the last 12 weeks of the study.[9]

At week 24, patients who received basal insulin and mealtime insulin human inhalation powder had a mean reduction in HbA_{1c} levels that achieved the prespecified noninferiority margin of 0.4% (**Table 1**). Patients who received insulin human inhalation powder demonstrated less reduction in HbA_{1c} levels than those receiving insulin aspart, and the difference was significant. In addition, more patients in the insulin aspart group achieved the target HbA_{1c} level of <7% compared with patients who received insulin human inhalation powder (Table 1).[9]

Type 2 Diabetes

A 24-week, double-blind, placebo-controlled study was conducted in 479 adults with type 2 diabetes whose disease was inadequately controlled with maximally tolerated doses of metformin only or with ≥2 oral antidiabetes agents. After a 6-week run-in period, 353 patients were randomized to receive either insulin human inhalation powder or an inhaled placebo powder without insulin. For the first 12 weeks, the insulin doses were titrated and were kept stable for the last 12 weeks of the study. The doses of oral antidiabetes agents were kept stable.[9] At week 24, treatment with insulin human plus oral antidiabetes agents provided a significantly greater mean reduction in HbA_{1c} levels compared with placebo (**Table 2**).[9]

Safety

The most common adverse reactions (≥2%) associated with insulin human inhalation powder include hypoglycemia, cough, and throat pain or irritation.[9]

Contraindications

The use of insulin human inhalation powder is contraindicated during episodes of hypoglycemia. It is also contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD). In addition, insulin human inhalation powder is contraindicated in patients with hypersensitivity to regular human insulin or any of the insulin human inhalation powder excipients.[9]

Drug Interactions

Drugs that affect glucose metabolism. The adjustment of insulin dosage and an increased frequency of glucose monitoring may be required with insulin human inhalation powder if it is coadministered with drugs that may increase the risk for hypoglycemia, or drugs that may increase or decrease the blood glucose–lowering effect of insulin human inhalation powder.[9]

Drugs that may affect hypoglycemia. The signs and symptoms of hypoglycemia may be reduced or absent when antiadrenergic drugs (eg, beta-blockers, clonidine, guanethidine, and reserpine) are coadministered with insulin human inhalation powder.[9]

Warnings and Precautions

Boxed warning. The prescribing information for insulin human inhalation powder contains a boxed warning stating that acute bronchospasm has been observed in patients with asthma and COPD who use insulin human inhalation powder. In addition, before initiating therapy with insulin human inhalation powder, a detailed medical history, physical examination, and spirometry should be performed to identify potential lung disease in all patients.[9]

Acute bronchospasm. Acute bronchospasm has been observed in patients with asthma and COPD. Spirometry should be performed in all patients before initiating

treatment with insulin human inhalation powder. This medication should not be used in patients with chronic lung disease.[9]

Change in regimen. Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose an individual to hypoglycemia or hyperglycemia. These changes should be made under close medical supervision, and the frequency of blood glucose monitoring should be increased. The coadministration of oral antidiabetic agents with insulin human inhalation powder may require adjustment.[9]

Hypoglycemia. Hypoglycemia may be life-threatening. The frequency of glucose monitoring should be increased with changes to insulin dosage, coadministered glucose-lowering medications, meal pattern, and physical activity, as well as in patients with renal or hepatic impairment and hypoglycemia unawareness.[9]

Decline in pulmonary function. Pulmonary function should be assessed before initiating therapy with insulin human inhalation powder, after 6 months of therapy, and annually, even in the absence of pulmonary symptoms.[9]

Lung cancer. Insulin human inhalation powder should not be used in patients with active lung cancer. In patients with a history of lung cancer or those who are at risk for lung cancer, the benefit of insulin human inhalation powder therapy should outweigh this potential risk.[9]

Diabetic ketoacidosis. More patients using insulin human inhalation powder experienced diabetic ketoacidosis in clinical trials than patients not using insulin human inhalation powder. Patients at risk for diabetic ketoacidosis should be monitored and changed to an alternate route of insulin delivery, if necessary.[9]

Hypersensitivity reactions. Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, such as insulin human inhalation powder. The use of this medication should be discontinued, and patients should be monitored and treated, if necessary.[9]

Hypokalemia. Hypokalemia may be life-threatening. Potassium levels should be monitored in patients at risk for hypokalemia, and these patients should be treated, if necessary.[9]

Fluid retention and heart failure with the concomitant use of thiazolidinediones. Patients with diabetes should be observed for the signs and symptoms of heart failure; dosage reduction or discontinuation of insulin human inhalation powder should be considered if heart failure occurs.[9]

Use in Specific Populations

Pregnancy. Insulin human inhalation powder should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.[9]

Nursing mothers. A decision should be made whether to discontinue nursing or to suspend the use of insulin human inhalation powder, because it has not been studied in lactating women.[9]

Pediatric use. Insulin human inhalation powder has not been studied in patients aged <18 years.[9]

Geriatric use. In clinical studies, no overall differences in safety or efficacy were observed between patients aged ≥65 years.[9]

Hepatic impairment. The effect of hepatic impairment on the pharmacokinetics of insulin human inhalation powder has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for human insulin inhalation powder in patients with hepatic impairment.[9]

Renal impairment. The effect of renal impairment on the pharmacokinetics of this insulin has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Frequent glucose monitoring and dose adjustment may be necessary in patients with renal impairment.[9]

Conclusion

The management of diabetes remains a challenge that requires a variety of risk-reduction strategies and different treatment options. The recent FDA approval of insulin human inhalation powder has made available a new treatment option for the treatment of adults with diabetes. In patients with type 1 diabetes, treatment with mealtime insulin human inhalation powder plus basal insulin met the prespecified noninferiority margin of 0.4% compared with treatment with insulin aspart plus basal insulin at 24 weeks. In patients with type 2 diabetes, treatment with insulin human inhalation powder plus oral antidiabetic drugs demonstrated a significantly greater reduction in HbA_{1c} levels versus placebo plus oral antidiabetic drugs at week 24. ■

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